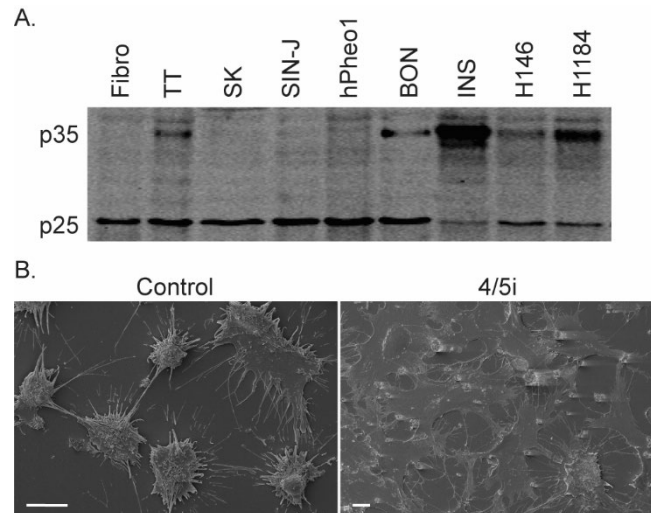**Supplementary Material**



**Fig. S1.** NE cells express p35/25 and respond to Cdk5 inhibition. (A) High contrast image of immunoblot of Cdk5 pathway components shown in Fig. 1A. (B) Scanning electron microscopy of hPHEO1 cells treated with 0.02% DMSO (Control) or 2 μM Indo A (4/5i) for 4 h. Scale bars = 10 μm.
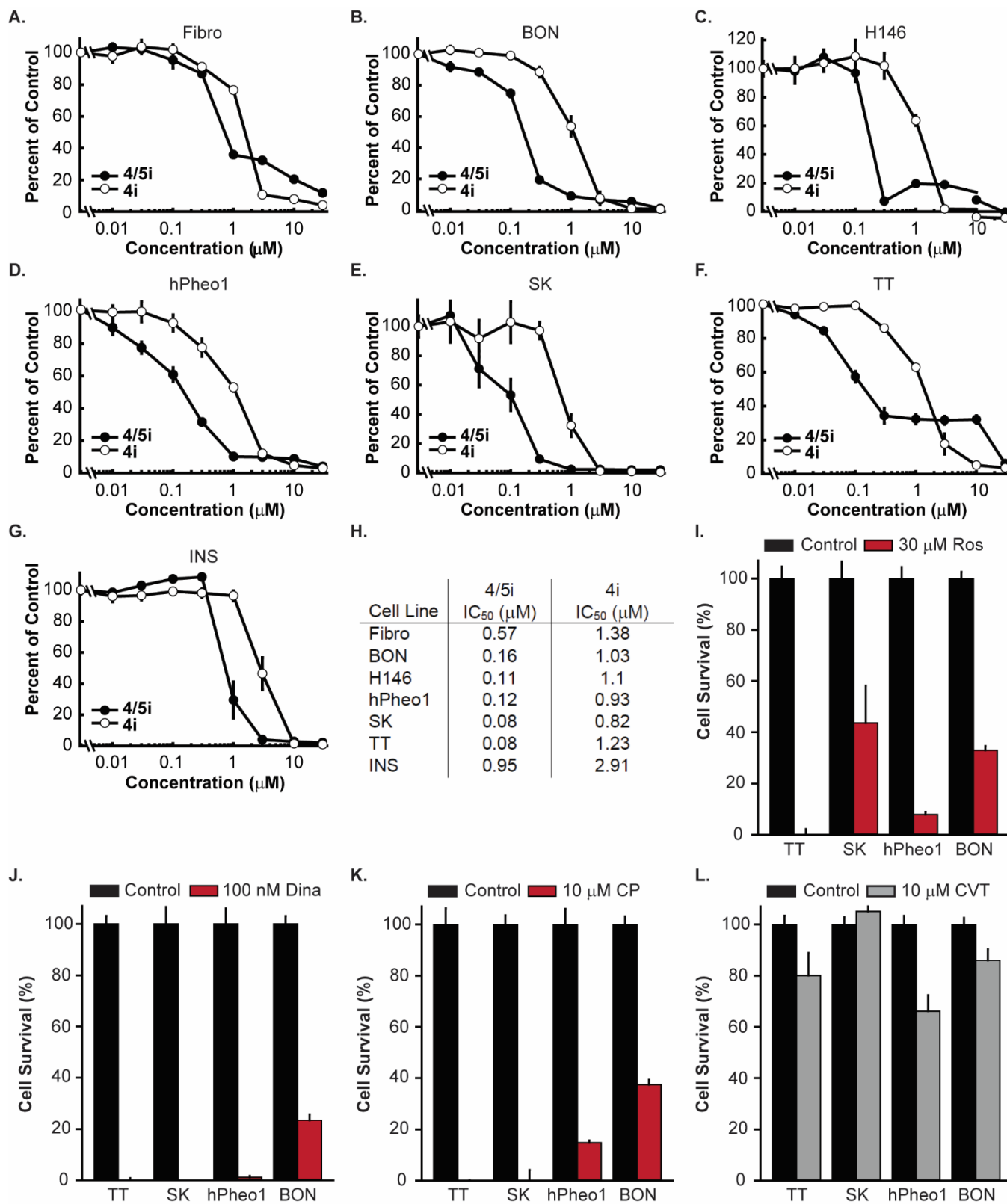
**Fig. S2.** Cdk5 inhibition blocks growth of NE cancer cells. (A-G) Cells were treated with increasing concentrations of Indo A (4/5i; n=6-9) and Indo B (4i; n=6-9) and monitored for effects on cell growth. (H) $IC_{50}$ values for each cell line and inhibitor were calculated by 4-parameter logistic regression. (I-L) NE cell

lines were treated with control or the Cdk inhibitor indicated; Roscovitine (Ros; n=4-8), Dinacyclib (Dina; n=6-8), CP681301 (CP; n=4-8), or CVT313 (CVT; n=8-12). All error bars represent SEM.
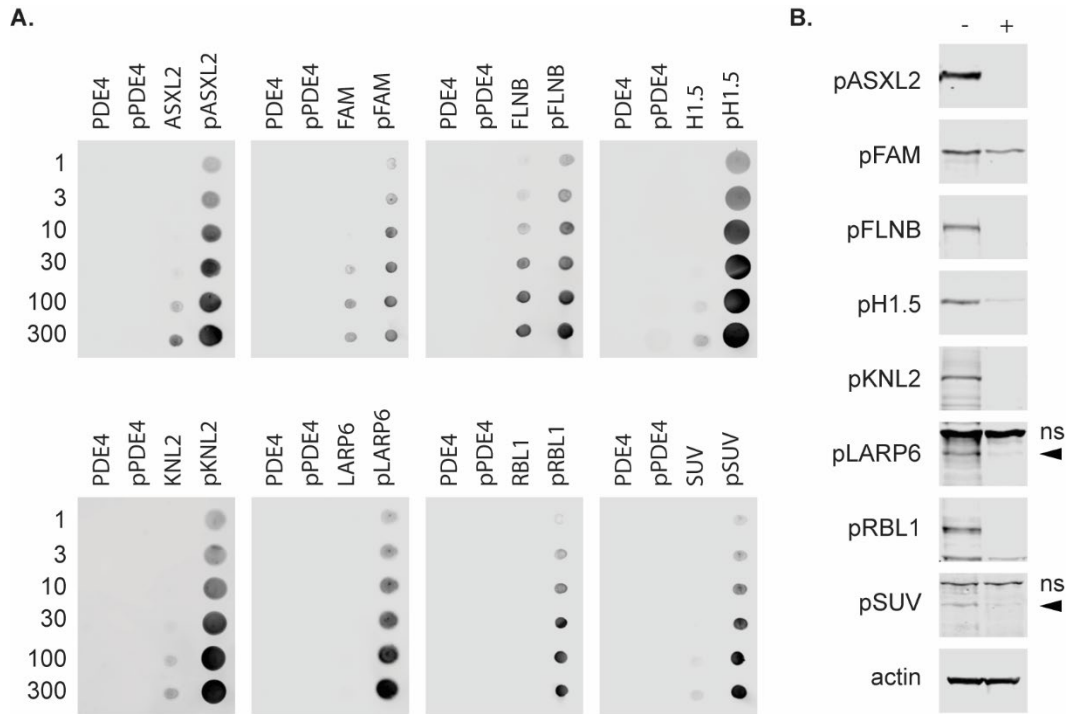
**Fig. S3.** Phosphorylation state-specific antibody validation. (A) Dot blots of nitrocellulose spotted with increasing pmol of PDE4 peptide, phospho-PDE4 (pPDE4) peptide, peptide of interest, or phospho-peptide of interest and probed with affinity purified anti-sera. (B) Immunoblot analysis of NSE-p25OE tumor lysate, treated with (+) and without (-) lambda protein phosphatase, probed with affinity purified anti-sera. Non-specific bands (ns), specific bands denoted by arrowheads where applicable.
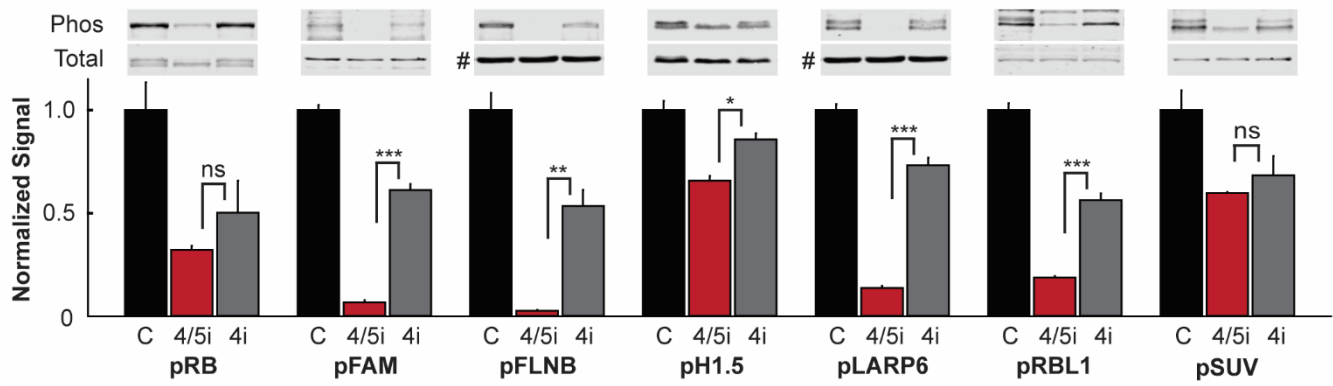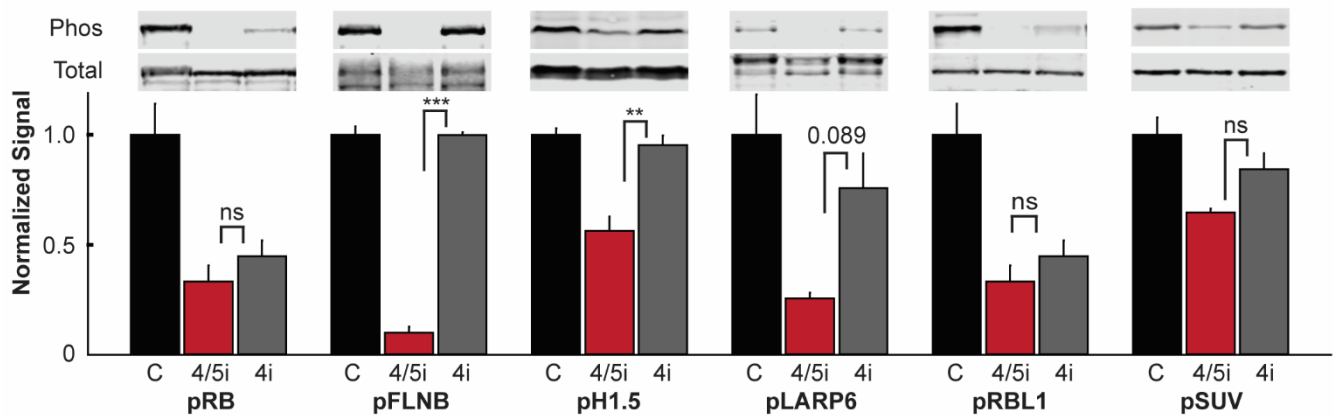
**Fig. S4.** Phosphoproteins are dependent on Cdk5 activity. Immunoblot analysis of phosphoproteins in TT cells (A) and SK cells (B) treated with 0.3% DMSO (Control), 2 μM Indo A (4/5i), or 2 μM Indo B (4i) for 4 h. For A, pFLNB and pLARP are normalized to actin (#); all others are normalized to each specific protein. All error bars represent SEM.
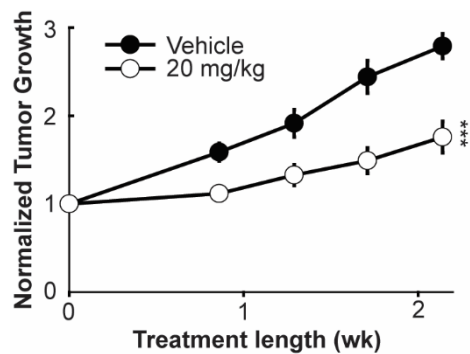
**Fig. S5.** Inhibition of Cdk5 activity suppresses growth of pancreatic NE tumors. Quantitation of tumor growth over time from caliper measurements of BON xenograft pancreatic NE tumor model mice treated with vehicle or 20 mg/kg BW Indo A. (n=8-9). Error bars represent SEM..
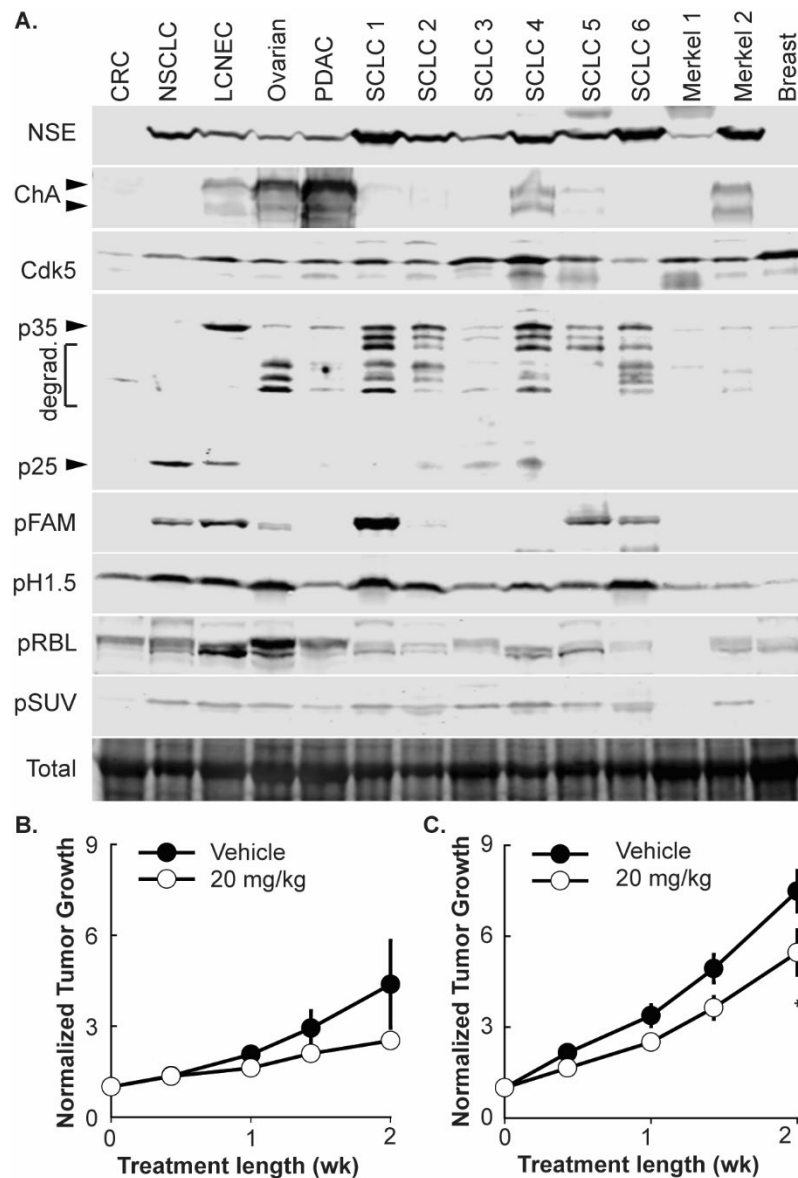
**Fig. S6.** Inhibition of Cdk5 activity suppresses growth of biomarker-positive NE tumors. (A) Immunoblot analysis of proteins and phosphoproteins in tumors from PDX model mice. (B-C) Quantitation of tumor growth over time from biomarker-negative Merkel 2 (B; n=5-6) and biomarker-positive LCNEC (C; n=8) PDX model mice treated with vehicle or 20 mg/kg BW Indo A (20 mg/kg). All error bars represent SEM.
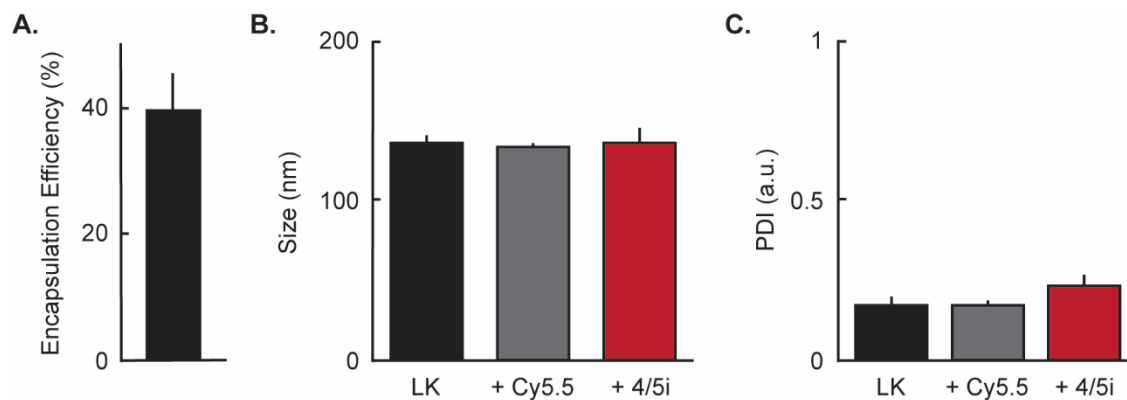
**Fig. S7.** Encapsulation of Indo A does not affect biophysical properties of LKs. (A) Entrapment efficiency of Indo A into LKs as determined by intrinsic Indo A fluorescence. (B-C) Dynamic light scattering analysis of LKs, Cy5.5 labeled LKs (+ Cy5.5), and Indo A loaded LKs (+ 4/5i) to determine size (B) and polydispersity (C). All error bars represent SEM.

**Table S1: Protein groups of peptides identified in LC-MS/MS of MTC mouse tumors.**

| # in Fig. 3D | Group | Percent of Total | Percent of Upregulated |
|---|---|---|---|
| 1 | Autophapy | 8.6 | 6.9 |
| 2 | Development and differentiation | 20.5 | 21.5 |
| 3 | Kinase (non-protein) | 15.9 | 18.3 |
| 4 | Other | 7.7 | 5.9 |
| 5 | Tumor Suppressor | 3.4 | 2.4 |
| 6 | Translation | 3.3 | 3.5 |
| 7 | Lipid binding | 6.5 | 3.8 |
| *8 | Apoptosis | 6.5 | 12.1 |
| *9 | Protease | 2.9 | 5.9 |
| 10 | Ub conjugation | 2.8 | 0.7 |
| 11 | Phosphatase | 5.4 | 4.5 |
| 12 | Intracellular structures | 5.3 | 3.1 |
| 13 | Protein Kinase signaling | 1.9 | 1.0 |
| 14 | Receptor/channel/surface protein | 1.8 | 0.3 |
| *15 | Adhesion/ECM | 1.5 | 2.8 |
| 16 | Cell Cycle regulator | 1.3 | 1.7 |
| *17 | DNA binding | 0.9 | 1.7 |
| 18 | Adaptor Scaffold | 0.9 | 0.0 |
| *19 | Miscellaneous Enzyme | 0.7 | 1.4 |
| 20 | G-protein or regulator | 0.6 | 0.7 |
| *21 | RNA processing | 0.6 | 1.0 |
| 22 | Transcriptional regulator | 0.5 | 0.3 |
| 23 | Unknown | 0.4 | 0.0 |
| *24 | Cytoskeletal | 0.1 | 0.3 |

* - enriched in upregulated (levels in growing/arrested tumors ≥ 2) vs. total population of peptides.

**Table S2: Growth inhibition by individual SIPs represented in Figure 3E.**

| # | SIP Target | Percent Growth ± SEM | | | |
|---|---|---|---|---|---|
| | | Fibro | SK | PHEO | BON |
| 1 | Control 1 (HBSS) | 100 ± 2.4 | 100 ± 2.7 | 100 ± 1.2 | 100 ± 0.7 |
| *2 | LIG1 | 122 ± 5.0 | 4 ± 0.6 | 4 ± 1.5 | 15 ± 1.2 |
| *3 | POLE | 116 ± 4.7 | 3 ± 0.4 | 38 ± 11.8 | 28 ± 1.3 |
| 4 | LIN9a | 166 ± 10.5 | 68 ± 16.2 | 43 ± 6.2 | 79 ± 1.7 |
| 5 | POLA1 | 80 ± 4.5 | 62 ± 15.6 | 18 ± 6.0 | 64 ± 2.2 |
| *6 | RBL1 | 137 ± 7.9 | 78 ± 10.6 | 14 ± 3.6 | 83 ± 1.2 |
| 7 | INADL | 124 ± 5.5 | 84 ± 16.5 | 57 ± 4.3 | 64 ± 1.3 |
| 8 | NCL | 121 ± 5.4 | 100 ± 6.2 | 72 ± 6.7 | 96 ± 2.1 |
| 9 | STMN1 | 123 ± 5.1 | 106 ± 8.4 | 84 ± 5.3 | 98 ± 2.0 |
| 10 | WHSC2 | 119 ± 5.2 | 67 ± 16.6 | 58 ± 6.8 | 89 ± 1.6 |
| 11 | SCAPER | 117 ± 5.7 | 97 ± 11.8 | 56 ± 6.4 | 94 ± 2.1 |
| 12 | SCC112 | 188 ± 4.4 | 49 ± 17.6 | 30 ± 4.7 | 33 ± 1.4 |
| *13 | H1.5 | 119 ± 6.9 | 56 ± 17.5 | 41 ± 9.9 | 82 ± 1.5 |
| 14 | APRIN | 121 ± 5.3 | 109 ± 6.0 | 79 ± 4.0 | 95 ± 2.7 |
| 15 | NUMA1 | 138 ± 11.0 | 71 ± 9.6 | 56 ± 5.7 | 93 ± 1.7 |
| *16 | LARP6 | 122 ± 5.6 | 10 ± 3.2 | 15 ± 5.4 | 33 ± 1.0 |
| 17 | MYBBP61A | 120 ± 6.5 | 93 ± 7.7 | 77 ± 6.2 | 97 ± 2.6 |
| 18 | WHSC1 | 114 ± 5.3 | 107 ± 9.7 | 83 ± 4.4 | 98 ± 1.4 |
| 19 | MGC4707 | 124 ± 5.7 | 93 ± 4.2 | 77 ± 4.5 | 98 ± 1.3 |
| 20 | ALDH2 | 109 ± 2.7 | 36 ± 10.6 | 68 ± 7.3 | 65 ± 1.1 |
| 21 | LIG1b | 107 ± 2.7 | 109 ± 3.7 | 84 ± 5.1 | 90 ± 1.9 |
| *22 | MTA2 | 140 ± 3.1 | 5 ± 0.9 | 1 ± 0.4 | 14 ± 1.3 |
| 23 | GTF3C1 | 107 ± 1.4 | 89 ± 19.0 | 40 ± 8.2 | 70 ± 2.7 |
| 24 | SPT5 | 107 ± 4.9 | 120 ± 4.3 | 79 ± 5.5 | 89 ± 2.9 |
| *25 | FLNB | 122 ± 7.0 | 0 ± 0.2 | 6 ± 1.8 | 5 ± 0.7 |
| 26 | IQCE | 116 ± 1.8 | 6 ± 1.9 | 38 ± 10.3 | 36 ± 1.2 |
| *27 | ASXL2 | 112 ± 1.2 | 4 ± 0.4 | 9 ± 3.3 | 20 ± 1.0 |
| *28 | SUV39H1 | 111 ± 1.5 | 3 ± 0.3 | 3 ± 1.1 | 23 ± 1.1 |
| 29 | SNXL3 | 112 ± 3.7 | 118 ± 3.0 | 87 ± 5.1 | 93 ± 2.3 |
| *30 | KNL2 | 158 ± 5.5 | 7 ± 5.0 | 1 ± 0.5 | 8 ± 1.0 |
| 31 | CASZ1 | 101 ± 2.9 | 114 ± 6.2 | 92 ± 3 | 95 ± 1.6 |
| 32 | SH3BP4 | 106 ± 2 | 91 ± 12 | 52 ± 8 | 83 ± 2.1 |
| 33 | HPCAL | 107 ± 2.5 | 109 ± 2.8 | 80 ± 5.5 | 88 ± 2.5 |
| 34 | ACSL4 | 105 ± 2.1 | 89 ± 5.4 | 64 ± 6.8 | 83 ± 2.3 |
| 35 | eIF3ep | 59 ± 5 | 0 ± 0.4 | 0 ± 0.3 | 3 ± 1 |
| 36 | EPLIN | 96 ± 1.9 | 95 ± 10.5 | 39 ± 7.4 | 81 ± 2.6 |
| *37 | MTA1 | 147 ± 5.5 | 52 ± 15.1 | 10 ± 2.7 | 47 ± 2.1 |
| 38 | Rb1a | 147 ± 7.4 | 41 ± 12.4 | 36 ± 3.5 | 43 ± 1.6 |
| 39 | USP24 | 123 ± 6.3 | 101 ± 13.4 | 78 ± 4.9 | 89 ± 1.7 |
| *40 | FBXL17 | 151 ± 2.1 | 1 ± 1 | 0 ± 0.1 | 0 ± 0.1 |

**Table S2 continued: Growth inhibition by individual SIPs represented in Figure 3E.**

| # | SIP Target | Percent Growth ± SEM | | | |
|---|---|---|---|---|---|
| | | Fibro | SK | PHEO | BON |
| *41 | SLBP | 124 ± 4.8 | 2 ± 0.2 | 16 ± 5.1 | 12 ± 1.4 |
| *42 | RIZ | 125 ± 5.3 | 0 ± 0.2 | 0 ± 0.1 | 0 ± 0.1 |
| 43 | RbBP6 | 115 ± 3.4 | 133 ± 10.3 | 88 ± 1.8 | 97 ± 1.7 |
| 44 | USP14 | 114 ± 4.4 | 126 ± 12.4 | 78 ± 6 | 94 ± 1.7 |
| 45 | eIF3eta | 41 ± 2 | 3 ± 1.4 | 9 ± 2.4 | 25 ± 1.2 |
| 46 | Rb1b | 116 ± 3.7 | 57 ± 17.3 | 34 ± 8.9 | 54 ± 3.3 |
| 47 | GPATCH8 | 117 ± 4.8 | 129 ± 9.1 | 79 ± 3.3 | 98 ± 2.2 |
| 48 | ELAVL1 | 110 ± 3.7 | 113 ± 23.3 | 67 ± 7.6 | 70 ± 3.8 |
| 49 | LIN9b | 119 ± 5.4 | 142 ± 11.8 | 78 ± 6.6 | 97 ± 1.9 |
| 50 | ABI1 | 111 ± 3.8 | 91 ± 19 | 52 ± 12 | 82 ± 1.7 |
| *51 | FAM53C | 112 ± 4.7 | 34 ± 11.3 | 57 ± 12 | 61 ± 1.5 |
| 52 | Control 2 (PEN tag) | 112 ± 2.9 | 138 ± 14.3 | 76 ± 5.9 | 94 ± 1.6 |

* selected as a hit

**Table S3: Pathway Enrichment Analysis on 15 selected hits.**

| Abbreviation | Ingenuity Canonical Pathways | -log(p-value) | Molecules | Color |
|---|---|---|---|---|
| AHRS | Aryl Hydrocarbon Receptor Signaling | 1.08 | RBL1 | Gray |
| ATMS | ATM Signaling | 1.23 | SUV39H1 | rosybrown |
| BCS | Bladder Cancer Signaling | 1.23 | SUV39H1 | indianred |
| BERP | BER pathway | 4.61 | POLE,LIG1 | firebrick |
| CCCR | Cell Cycle Control of Chromosomal Replication | 3.3 | POLE,LIG1 | darkred |
| CCR | Cyclins and Cell Cycle Regulation | 1.31 | SUV39H1 | orangered |
| CES | Caveolar-mediated Endocytosis Signaling | 1.36 | FLNB | darkorange |
| CMLS | Chronic Myeloid Leukemia Signaling | 2.63 | SUV39H1,RBL1 | orange |
| DDSBRHR | DNA Double-Strand Break Repair by Homologous Recombination | 2.05 | LIG1 | olive |
| DMTRS | DNA Methylation and Transcriptional Repression Signaling | 3.68 | MTA2,MTA1 | olivedrab |
| EMSE | Estrogen-mediated S-phase Entry | 1.78 | RBL1 | gold |
| GS | Glioma Signaling | 2.56 | SUV39H1,RBL1 | yellow |
| GSCCR | Cell Cycle: G1/S Checkpoint Regulation | 3.13 | SUV39H1,RBL1 | seagreen |
| ILKP | ILK Signaling | 0.928 | FLNB | springgreen |
| MMC | Molecular Mechanisms of Cancer | 1.61 | SUV39H1,RBL1 | turquoise |
| NERP | NER Pathway | 2.75 | POLE,LIG1 | mediumturquoise |
| NSCLCS | Non-Small Cell Lung Cancer Signaling | 1.26 | SUV39H1 | teal |
| OCS | Ovarian Cancer Signaling | 1.03 | SUV39H1 | deepskyblue |
| PAS | Pancreatic Adenocarcinoma Signaling | 1.12 | SUV39H1 | steelblue |
| PCS | Prostate Cancer Signaling | 1.18 | SUV39H1 | dodgerblue |
| PKS | Protein Kinase A Signaling | 0.666 | FLNB | slateblue |
| RBDDR | Role of BRCA1 in DNA Damage Response | 1.3 | RBL1 | mediumslateblue |
| SCLCS | Small Cell Lung Cancer Signaling | 1.27 | SUV39H1 | darkorchid |
| SSP | Sirtuin Signaling Pathway | 0.799 | SUV39H1 | fuchsia |
| VEVEP | Virus Entry via Endocytic Pathways | 1.15 | FLNB | deeppink |

**Table S4: Index Scores for characteristics of PDX models of cancer.**

PDX Models

| Group | LCNEC | Merkel 1 | Merkel 2 | NSCLC | SCLC 1 | SCLC 2 | SCLC 3 | SCLC 4 | SCLC 5 | SCLC 6 | Breast | CRC | Ovarian | PDAC |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| p25 | 2 | 0 | 0 | 3 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| p35 | 3 | 0 | 0 | 1 | 1 | 2 | 0 | 2 | 0 | 1 | 0 | 0 | 1 | 0 |
| Cdk5 | 1 | 1 | 1 | 0 | 1 | 1 | 2 | 3 | 1 | 0 | 2 | 0 | 0 | 1 |
| **Cdk5 pathway** | **6** | **1** | **1** | **4** | **2** | **3** | **2** | **5** | **1** | **1** | **2** | **0** | **1** | **1** |
| ChA | 1 | 0 | 2 | 0 | 0 | 0 | 0 | 2 | 0 | 0 | 0 | 0 | 3 | 3 |
| NSE | 1 | 0 | 2 | 1 | 3 | 2 | 1 | 2 | 1 | 3 | 0 | 0 | 0 | 1 |
| **NE markers** | **2** | **0** | **4** | **1** | **3** | **2** | **1** | **4** | **1** | **3** | **0** | **0** | **3** | **4** |
| pH1.5 | 2 | 0 | 0 | 2 | 3 | 3 | 1 | 1 | 2 | 3 | 0 | 0 | 3 | 0 |
| pFAM | 1 | 0 | 0 | 1 | 3 | 0 | 0 | 0 | 1 | 0 | 0 | 0 | 0 | 0 |
| pRBL1 | 3 | 0 | 0 | 1 | 0 | 0 | 0 | 1 | 1 | 0 | 0 | 0 | 3 | 2 |
| pSUV | 2 | 0 | 1 | 2 | 2 | 1 | 2 | 3 | 3 | 1 | 0 | 0 | 2 | 1 |
| **Biomarkers** | **8** | **0** | **1** | **6** | **8** | **4** | **3** | **5** | **7** | **4** | **0** | **0** | **8** | **3** |

Models initially classified as NE are shown in white. Models initially classified as non-NE are shown in grey.